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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,863	11/19/2001	James G. Karras	ISPH-0618	1531

7590 02/18/2005

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,863	KARRAS ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The Declaration filed on 12-13-2004 under 37 CFR 1.131 is sufficient to overcome the Lorenz et al. (WO 00/77204 A1) reference.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-2, 4-6 and 11-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Lorenz et al. (US 6,740,487).

Lorenz et al. anticipate claims 1-2, 4-6, and 11-12 by describing modified oligomeric compounds of 8 to 50 nucleobases in length targeted to nucleic acid encoding Toll like receptor 4 (TLR4). The nucleic acid encoding human TRL4 is described as GenBank Accession No. U88880, see col. 3, Figure 1 description. This sequence is the same sequence described as SEQ

ID NO: 3 in the instant application. The antisense oligonucleotides of Lorenz et al. may comprise modified nucleotides, modified sugars, and internucleoside linkages, including phosphorothioate modified linkages, see col. 5, lines 35-55. Moreover, Lorenz et al. teach that when using the oligonucleotides described in this reference as probes or treatment, they are preferably contain no less than 85% sequence identity with its target nucleic acid (see col. 6, 1st ¶).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-2, 4-14, and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorenz et al. (US 6,740,487) in view of Monia et al. (US Patent NO. 6,114,517), and Taylor et al.

The discussion of Lorenz et al. as set forth above is incorporated here. However, Lorenz et al. does not teach the chimeric oligonucleotides, specific sugar and nucleobase modifications, or the colloidal dispersion system composition claimed by Applicants. Additionally, Lorenz et al. does not teach the design of antisense oligonucleotides specifically hybridizable to the start or stop region, the coding region, the 5'UTR or the 3' UTR. Moreover, Lorenz et al. does not teach antisense oligonucleotides that inhibit Toll-like receptor 4 by at least 50% or 70%.

Monia et al. teach that the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 41-43),

2'-O-methoxyethyl sugar modifications (col. 10, line5), 5-methylcytosine modified nucleobase (col. 10, line 31-32), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 11, line 51). The modified or substituted oligonucleotides of Monia et al. are preferred over native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 8, lines 2-6).

The antisense oligonucleotides of Monia et al. are preferably designed to target the following regions of an mRNA: the coding region, the 5' untranslated region (5'UTR), 3' untranslated region (3'UTR), and the translation initiation (start region) and the translation termination regions (stop region), see col. 5-6). Additionally, Monia et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 15, lines 19-41).

Taylor et al. (1999) teach that by using high affinity oligomers and a bioinformatics program to select accessible sites in a mRNA target, the skilled artisan would only need to screen from 3-6 oligomers to find one that inhibits the target mRNA with 66-95% efficiency (see page 565, 1st paragraph).

It would have been obvious to one of ordinary skill in the art, at the time of the instant invention, to modify the teachings of Lorenz et al. with the teachings of Monia et al. in the design of the antisense compounds according to the present invention and the composition according to present invention comprising pharmaceutically acceptable carrier or diluent, and

further comprising a colloidal dispersion system. One of ordinary skill in the art would have been motivated to make these modifications because Monia et al. teach that antisense compound modified according to the present invention and compositions designed according to the present invention would enhance the stability of oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

Additionally, in regards to wherein the antisense compounds of the present invention must reduce the expression of Toll-like receptor 4 (TLR4) mRNA by at least 50% or 70%, according to Taylor et al. (December 1999), one of skill in the art at the time the instant invention was made, using high affinity chimeric oligomers and a bioinformatics program to select accessible sites, would only need to screen 3-6 oligomers per target gene to find one that inhibits a gene with 66-95% efficiency. Absent evidence to the contrary the antisense compounds designed according to the teachings of Lorenz et al. in view of Monia et al., would inherently possess the same functional activity as Applicant's claimed compounds, particularly in view of Taylor who teach such would have been feasible.

Therefore, the invention as a whole, at the time of the instant invention, would have been *prima facie* obvious of Lorenz et al. in view of Monia et al. and Taylor et al.

Claim Rejections - 35 USC § 112

5. Claim 11 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. Applicant's arguments filed 12-01-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by way of amendment. In particular, Applicants argue that the current amendment of claim 1 to recite that the compound is targeted to a nucleic acid molecule encoding TLR4 of SEQ ID NO: 3, renders the rejection moot. Contrary to Applicant's assertions, original claim 11 does not recite dependency from claim 1. Therefore, Applicant's amendment to claim 1 does not overcome the prior rejection of claim 11. Although, Applicants provide only a description of compounds according to the present invention which target nucleic acid encoding human TLR4 according to SEQ ID NO: 3, this description does not provide evidence that Applicants were in possession of the full scope of compounds that are 8 to 50 nucleobases in length which specifically hybridize to all genomic variants of TLR4 from all species of organisms, including all polymorphic, allelic, and splice variants of this gene. Moreover, claim 11 requires the identification of "active sites" on all forms of TLR4. According to the specification as filed, at page 9, lines 26-35, the "active sites" or preferential target sites to which antisense and other compounds of the invention hybridize to and inhibit expression of the TRL4, are identified through experimentation. Therefore, the compounds according to the present invention which target SEQ ID NO: 3 can not be used to predict the structures of compounds which would be effective to "specifically hybridize" to forms of TLR4 isolated from other organisms since functional antisense compounds can only be identified empirically.

See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the

claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Additionally, MPEP § 2163 [R-1] states "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Applicant's specification does not provide a sufficient description of all embodiments encompassed by the claimed compounds, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. Moreover, it is apparent that further experimentation is required to identify the structures of all embodiments encompassed by the instant claims. Therefore, the specification does not describe the claimed compounds in such

full and concise terms so as to indicate that the applicant had possession of the full scope of compounds encompassed by the instant claims at the time of filing of this application.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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